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Review

Do antioxidants impair signaling by reactive oxygen species and lipid oxidation products?

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ABSTRACT

Oxidative modification of biologically essential molecules by reactive oxygen and nitrogen species (ROS/RNS) has been implicated in the pathogenesis of various diseases. At the same time, roles of ROS/RNS as physiological signaling messenger have been established. Lipid oxidation products also have two faces. It is argued that the radical scavenging antioxidants taken from diet or supplement may impair such beneficial effects of ROS/RNS and lipid oxidation products. However, it is unlikely that antioxidants impair physiologically important signaling, since the antioxidants do not scavenge signaling ROS/RNS nor do they inhibit the formation of signaling molecules. Lipid peroxidation products are not produced on purpose and inhibition of lipid peroxidation by antioxidants should be beneficial for maintenance of health and reducing disease risk.

1. Introduction

It was originally accepted that reactive oxygen/nitrogen species, ROS/RNS, exert deleterious effects by oxidizing biologically essential molecules such as lipids, proteins, carbohydrates, and DNA [1]. Compelling data show clearly that ROS/RNS formed in vivo and imported from outside induce oxidative damage of cellular membranes, tissues, and enzymes, which may eventually lead to disorders and diseases such as atherosclerosis, neurological diseases, and cancer. Later studies revealed, however, that ROS/RNS may act also as cellular signaling messenger in physiological settings with important regulatory functions [2–8]. Hydrogen peroxide is considered to be the most important signaling messenger considering the specificity of its production, reaction and removal [7]. ROS/RNS produced in an exquisitely controlled and regulated manner function as a regulator of gene expression, activator of receptors and nuclear transcription factors, and inducer of adaptive response. Thus, ROS/RNS act as a double edged sword by exerting both harmful and beneficial effects.

Likewise, accumulating evidence shows that lipid oxidation products have also two faces [9,10]. Free radical-mediated lipid oxidation, termed lipid peroxidation (LPO), has been implicated in the pathogenesis of various diseases. LPO induces disturbance of fine structure, alteration of integrity, fluidity, and permeability, and functional loss of biomembranes, modifies low density lipoprotein (LDL) and high density lipoprotein (HDL) to pro-atherogenic and pro-inflammatory forms, and generates potentially toxic products. Further, LPO products have been shown to be mutagenic and carcinogenic. The reactive carbonyl compounds, the secondary products of LPO, modify proteins and DNA bases [11]. Thus LPO has been implicated as the underlying mechanisms in numerous disorders and diseases such as cardiovascular diseases, cancer, neurological disorders, and aging [12,13]. Consistent with this notion, numerous studies show increased levels of LPO products in the biological fluids and tissues from the patients compared with healthy subjects [9,13].

However, recent studies show that LPO products are also capable of acting as signaling mediator and induce adaptive response to up-regulate defense capacity, in many cases, through nuclear factor erythroid 2-related factor 2 (Nrf2)–Kelch-like ECH-associated protein 1 (Keap1) system [9,10,14]. Recently, it has been argued that excess antioxidants may impair signaling of ROS/RNS and LPO products [15–17]. This brief article tries to address this issue.

2. Specific and random lipid oxidation

Lipid oxidation is taking place constantly in vivo and in fact considerable levels of multiple lipid oxidation products are found in biological fluids and tissues from healthy humans as well as various disease patients [9,18,19]. Lipids are oxidized by multiple

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oxidants, that is, enzymes, free radicals, and non-radical, non-enzymatic oxidants.

Enzymes such as cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP) oxidize unsaturated fatty acids to give physiologically important signaling messenger [20]. Arachidonic acid, one of the major constituents in cell membranes, is released from membrane phospholipids stores by phospholipase A2 which is activated by specific and non-specific stimuli. Arachidonic acid is oxidized by three principal pathways to form an important family of oxygenated products collectively termed eicosanoids, having potent bioactive signaling capacity. Over a hundred different eicosanoids have been identified. They are prostaglandins (PG) and thromboxane, collectively termed prostanoids, formed by COX, leukotrienes (LT), hepoxilins (HX), and lipoxins (LX) by LOX, and epoxyeicosatrienoic acid (EET) by CYP enzymes. In addition, LOX and CYP oxidize arachidonic acid to give hydroperoxyeicosatetraenoic acid (HPETE) and hydroxyeicosatetraenoic acid (HETE) respectively. Inflammation is a defensive response to injury and infection, but excessive or sustained inflammation contributes to a range of acute and chronic human diseases. Some polyhydroxy-fatty acids such as resolvins and protectins derived from EPA and DHA have been shown to play a pivotal role as novel mediators in the resolution of inflammation to return to homeostasis [21].

Enzymatic oxidation products of cholesterol have been shown to exert multiple physiological effects [22]. 22(*R*)-Hydroxycholesterol, a ligand for the liver X receptor, regulates the expression of the genes involved in cholesterol and fatty acid homeostasis, while 25-hydroxycholesterol regulates cholesterol synthesis. 24(*S*)-Hydroxycholesterol produced by cholesterol-24*S*-hydroxylase (CYP46A1) plays an important role in the homeostasis of cholesterol in the brain [23].

The characteristic feature of enzymatic oxidation is *specificity*. Each enzyme oxidizes specific substrate to give *regio*-, *stereo*- and *enantio*-specific products. Furthermore, the enzymatic oxidation is in general tightly programmed and regulated. On the other hand, free radical mediated LPO proceeds randomly to give diverse products. For example, LPO of arachidonic acid gives mixtures of *racemic* 5-, 8-, 9-, 11-, 12-, and 15-*cis,trans*- and *trans,trans*-HPETE, while 15-LOX gives 15(*S*)-*cis*,*trans*-HPETE exclusively. Free radicals attack proteins and DNA non-specifically as well as lipids.

Lipids, above all the polyunsaturated fatty acids (PUFAs), are vulnerable to free radical attack and readily oxidized by a chain mechanism in which lipid peroxyl radicals act as chain propagating species [9,24]. Lipid peroxyl radicals attack bis-allylic hydrogens of PUFA non-specifically. Both free and ester forms of PUFAs are oxidized by free radicals by the same mechanisms to give lipid hydroperoxides as major primary products, which are reduced by glutathione peroxidases and selenoprotein P to the corresponding hydroxides. Lipid hydroperoxides are decomposed by transition metal ions such as iron and copper to yield alkoxyl radicals, which may abstract hydrogen to give hydroxides or undergo β-scission to give short chain products including α,β-unsaturated carbonyl compounds. Multiple short chain oxidation products such as 4-hydroxy-2-nonenal (HNE) have been identified in biological fluids and tissues [11]. The β-scission of alkoxyl radicals is the major reaction to yield fragmented products in vivo. For those fatty acids having three or more double bonds, intramolecular addition of peroxyl radicals proceeds in competition with intermolecular hydrogen atom abstraction to give prostaglandin type cyclic products such as isoprostanes, isofurans, and neuroprostanes [24]. Isoprostane is accepted as the most reliable biomarker for LPO in vivo [18,19]. Thus, free radical mediated LPO produces diverse products. It is noteworthy that the relative importance of many competing reactions and distribution of LPO products are determined by many factors at the reaction site and difficult to be regulated.

3. Dual biological effects of lipid peroxidation products

There is now ample evidence that LPO proceeds in vivo to produce diverse products, which is associated with the progress of many diseases. For example, the oxidative modification of low density lipoprotein (LDL) and high density lipoprotein (HDL) has been accepted as an important initial event of atherosclerosis [12]. The oxidized LDL contains multiple oxidation products of cholesteryl esters, phospholipids, and cholesterol and their breakdown products. The levels of these oxidation products are associated with the atherogenesis of oxidized LDL and the progress of atherosclerosis.

The association between the levels of LPO products and liver diseases has also been reported. In the animal model experiments of fatty liver disease, the level of *trans*,*trans*-hydroxyoctadecadienoic acid (HODE), biomarker of LPO, correlated well with the increase in triglyceride and concomitant decrease in phospholipid in the liver and also with the accumulation of fat droplet [25]. It was reported that plasma isoprostane was significantly elevated in non-alcoholic fatty liver disease (NAFLD) patients (11.9 pg/ml, $n = 14$) as compared to healthy controls (6.3 pg/ml, $n = 38$) [26]. Further, it was reported that racemic HODE, a footprint of LPO, might be used as a marker of NAFLD [27].

The α,β-unsaturated carbonyl compounds such as HNE, acrolein, and 15-deoxyDelta prostaglandin J2 (15-dPGJ_2) react in Michael addition across its carbon–carbon double bond with a variety of cellular components including proteins and DNA. The reaction products of HNE, acrolein, and 15-dPGJ_2 with proteins have been detected in the tissues of patients and experimental animals for various diseases [11,28].

Many LPO products are cytotoxic but it has been found that at sublethal concentrations they are capable of inducing adaptive response to enhance cell tolerance against forthcoming oxidative stress. Such adaptive response was observed for chemically stable LPO products, such as HODE, lyso PC, hydroxycholesterol, and epoxycholesterol, as well as chemically active LPO products such as α,β-unsaturated carbonyl compounds [29–31]. The pretreatment of cells with sublethal concentrations of these LPO products enhanced cytoprotective capacity against the subsequent oxidative stress by, for example, hydrogen peroxide, 6-hydroxydopamine, HPODE, and 7-hydroxycholesterol [29–31]. In Table 1 are summarized the examples of enhancement of cytoprotective capacity induced by a pretreatment of LPO products against subsequent oxidative insult. Thus, it is clear that LPO products may also exert both harmful and beneficial effects.

Table 1
Enhancement of cytoprotective capacity induced by lipid peroxidation (LPO) products against subsequent oxidative stimuli.

LPO products	Second stimuli
PC hydroperoxide	6-Hydroxydopamine
HODE	HPODE
7-α,β-Hydroxycholesterol	7-α,β-Hydroxycholesterol
5,6-Epoxycholesterol	Cumene hydroperoxide
15-dPGJ_2	Hydrogen peroxide
HNE	Glutamate
Lyso	PC SIN-1
γ-Tocopheryl quinone	MPTP
Hydrogen peroxide	γ-Ray irradiation

Pretreatment of cultured cells with LPO products shown in the left side increased cellular tolerance against the subsequent second stimuli shown in the right side. PC: phosphatidylcholine; H(P)ODE: hydro(pero)xyoctadecadienoic acid; HNE: hydroxy-2-nonenal; SIN-1: 3-morpholinosydnonimine; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

4. Adaptive response induced by lipid oxidation products

Compelling evidence shows that cells have the capacity to adapt to oxidative stress through cell signaling mechanisms. Radiation hormesis, a putative stimulatory effect of low level ionizing radiation, has been ascribed to protective feedback systems that, upon exposure to low concentrations of toxins, proceed to stimulate metabolic detoxification and repair networks [32]. It was found some time ago that cells being exposed to low levels of hydrogen peroxide are able to survive the subsequent normally lethal oxidative stress, by increasing transcription of stress-related genes, antioxidant defense genes, and/or repair enzymes [33,34].

In addition to hydrogen peroxide, and in spite of the data suggesting the involvement of LPO in the pathogenesis of various diseases and also the association between the levels of LPO products and disease state, LPO products have been shown to exert beneficial effects under certain circumstances. As described above, chemically stable LPO products as well as α,β-unsaturated carbonyl compounds act as inducer of adaptive response. These LPO products induce the synthesis of glutathione and expression of antioxidant enzymes such as heme oxygenase (HO-1), glutathione S-transferase (GST), thioredoxin reductase (TR), and NAD(P)H quinone oxidoreductase 1 (NQO1) by Nrf2-Keap1 system [14,35]. LPO products enhance the release of Nrf2 from Keap 1 and translocation of Nrf2 into the nucleus, where it binds to electrophile response element (EpRE) and up-regulates the transcription of target genes. Nitro-fatty acids such as nitro-oleic acid has been detected in human fluids [36]. Although not an oxidation product, they are formed by the reaction of unsaturated fatty acids with nitrogen dioxide radical and they are claimed to improve endothelial dysfunction through enhancing NO signaling and blocking vascular smooth muscle proliferation, inflammation, and maladaptive remodeling [37]. It was found also that low levels of oxidized LDL were cytoprotective through induction of intracellular glutathione [38,39].

5. Role of antioxidants

Mammals have evolved with an elaborate defense network against oxidative stress, in which multiple antioxidant compounds and enzymes with different functions exert their respective roles [40,41]. Among others, radical scavenging antioxidants, referred to simply antioxidants hereafter, play their roles by scavenging reactive free radicals to protect biologically essential molecules from oxidative modification. The beneficial effects of these antioxidants have been supported by epidemiological studies [42], although many randomized, cross-over, intervention studies and their meta analysis on the effects of antioxidants on chronic diseases gave contradictory and confusing results [43]. This may be ascribed, at least in part, to the complex effects of oxidative stress on pathogenesis and role of antioxidants in human health [44].

The importance of inhibition of free radical mediated oxidation of biological molecules in the pathogenesis of diseases is supported by an association of progress of diseases with an increase in the levels of lipid peroxidation products and proteins modified by them. An increase in tocopherylquinone and 5-nitro-γ-tocopherol observed in patients and experimental animals under oxidative stress suggests that vitamin E acts as a radical scavenging antioxidant [45].

In addition to these direct antioxidant effect, many antioxidant substances act as a cellular mediator to enhance the expression of antioxidant and detoxifying enzymes by Nrf2-Keap1 system [46,47]. The physiological importance of this system has been shown by the experimental evidence that Nrf2 knockout mice are more prone to oxidative stress [48].

It was argued recently that the excess removal of ROS/RNS and inhibition of lipid peroxidation by dietary antioxidants such as vitamin E may block beneficial actions of physiological signaling processes and that some antioxidants at high doses may be harmful [15–17]. However, it should be emphasized that the radical scavenging antioxidants such as vitamins E and C do not scavenge physiologically important signaling ROS such as hydrogen peroxide and superoxide, nor do they inhibit the enzymatic lipid oxidation. These antioxidants are not potent inhibitor of myeloperoxidase-mediated reactions [49]. It is unlikely that these antioxidants even at high doses impair physiological signaling by ROS/RNS and lipid oxidation products.

It is evident that lipid oxidation proceeds in vivo by both free radical and non-radical mechanisms. Appreciable levels of lipid oxidation products are found in biological fluids and tissues from healthy subjects. Many studies show the involvement of lipid oxidation products in both physiological and pathological settings and it is now generally accepted that they function as signaling mediators in vivo. However, in order to function as physiologically essential signaling messenger, the formation, reaction, and metabolism should be strictly regulated and controlled. This may be possible for enzymatic reactions, but it is difficult to control the time, site, and amount of formation of free radicals and also to regulate the reaction pathways. The lack of regulation and specificity in free radical formation and reactions makes it difficult for LPO products to act as physiologically essential signaling messenger. LPO mediated by peroxyl radicals cannot be programmed nor regulated and its products are not considered to be formed on purpose. The adaptive response induced by LPO products is thought as a protective response of the organisms to xenobiotics. The antioxidants do not impair physiologically essential signaling pathways and the inhibition of free radical mediated LPO should be beneficial.

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